sulfonamide, sulfone, sulfite, sulfoxide, sulfide, hydroxylamine, methylene (methylimino), methyleneoxy (methylimino), methoxyethyl, C_5-substituted nucleotide and methyloxyethyl.

THE REMARKS

Amendments:

Claims 92 and 109 have been amended to add limitations that were in the previously allowed claims in the parent application of U.S. Serial No. 09/093,972. Support for this amendment is found in said U.S. Parent Application, as well as, for example, on page 2, line 35 to page 3, line 17 in the instant application.

Applicant respectfully contends that the amendments will place the application in condition for allowance. No new matter is added in any of the above amendments and the examiner is respectfully requested to enter the amendments and reconsider the application.

Rejection of Robinson Amendment:

The Examiner has improperly rejected the Robinson Declaration (pursuant to 37 C.F.R. § 1.132), filed November 11, 2003, for allegedly providing data that was not part of the specification as originally filed. Applicant respectfully traverses this rejection for the following reasons, and ask that the Robinson Declaration be properly entered and fully considered by the Examiner.

Firstly, Applicant believes that the Examiner has improperly commented on the Robinson Declaration. It is not clear from the Office Action Response of February 11, 2004, whether the Examiner had proper signatory authority in dealing with 37 C.F.R. § 1.132 declarations. Pursuant to MPEP Sections 716 and 1004, only a Primary Examiner has signatory authority to comment on Declarations submitted under 37 C.F.R. § 1.132. Therefore, the Examiner's review and rejection of the Declaration is not valid, and the Declaration should be properly considered, and entered, by the Primary Examiner.

Secondly, Applicant asserts that the 37 C.F.R. § 1.132 Declaration was incorrectly dismissed for improper reasons. The Examiner dismissed the Declaration for allegedly setting forth data that was not "disclosed in the specification as originally filed." *See* Office Action, pg. 3. The Examiner furthermore cites as an example that oligonucleotide EPI-4067 was not disclosed in the specification as filed. The Examiner further contends that one of ordinary skill in the art would not have been

able "to produce the results obtained in the Declaration without first undertaking trial and error experimentation in order [to] identify the particular antisense oligonucleotides used in the experiments described in the Declaration." *Id.*

The Examiner, in concentrating on the EPI-4067 example, fails to properly consider the two other examples present in the Declaration. For example, the Examiner fails to comment on Example 1, which details experimental results for Bradykinin B2 (see ¶5 of the Declaration) that were *already known to those of ordinary skill in the art* at the time of filing. The Examiner treats the eotaxin disclosure similarly, and therefore improperly discounts the additional technical disclosure within the Declaration.

Moreover, Applicant asserts that the Examiner confuses the issue of "outside the scope of the claims," as in a 35 U.S.C. § 101 new matter rejection, and what is permissible as a disclosure in a 37 C.F.R. § 1.132 Declaration. Applicant reminds the Examiner that Declarations providing supporting evidence "within the scope of the **claims**" and not what is disclosed in the specification or examples, should be properly considered. *See In re Brana*, 51 F.3d 1560, 1567 (Fed. Cir. 1995). In the instant application, the pending claims recite methods for treating asthma with antisense oligonucleotides (see Claim 92 and 109). Therefore, the oligonucleotide EPI-4067 is within the scope of the claims because it is an antisense oligonucleotide for treating asthma. The Examiner, therefore, failed to properly consider the disclosure within the Declaration.

Thirdly, the Examiner failed to comment or give any weight to the comments in ¶8 regarding the unobviousness of the instant invention over the prior art. As stated, the declarant Cynthia B. Robinson, Vice President of Clinical Development at EpiGenesis Pharmaceuticals, Inc., stated that the results obtained using "the present invention provided unexpectedly superior results of efficacy as compared to the results one would expect if the oral or injectable treatment were used. MPEP § 716 requires an Examiner to "personally review and decide whether affidavits or declarations submitted under 37 C.F.R. § 1.132 for the purpose of traversing grounds of rejection are responsive to the rejection and *present sufficient facts to overcome the rejection*" (emphasis added). The Examiner clearly did not meet these requirements, and therefore failed to properly consider the disclosure within the Declaration.

For the above reasons, the Robinson Declaration should be fully considered and properly entered.

35 U.S.C. § 112, 2nd Paragraph Rejection

The Examiner rejected Claims 99-100, 104, 107, 117 and 124 for allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as his invention. This rejection is traversed in part and overcome in part in view of the amendments.

The Examiner alleges Claim 99 recites a vague and indefinite limitation of "wherein the pharmaceutical composition is administered by inhalation directly to the airway or lung of the subject." Applicant has amended the claim to remove "airway or" from the claim. Therefore, the Examiner should withdraw the rejection of Claim 99.

The Examiner alleges Claims 100 and 117 recite a vague and indefinite phrase "antisense to the initiation codon, the coding region or the 5' or 3' intron-exon junction of a target polypeptide." Applicant has amended the claim to now recite "antisense to the initiation codon, the coding region or the 5' or 3' intron-exon junction of a nucleic acid encoding a target polypeptide," which obviates the rejection. In addition, one of ordinary skill in the art would know precisely that the phrase "5' or 3' intron-exon junction" refers to the coding nucleic acid, however in the interest of expediting prosecution, applicants have amended this claim to obviate the rejection.

The Examiner alleges Claims 104 and 121 allegedly lack sufficient antecedent basis for the term "lung inflammation." Applicant has amended Claims 92 and 109, for which Claims 104 and 121 depend on, to recite the phrase "and/or lung allergy(ies) and/or inflammation," which obviates the rejection. Therefore, the Examiner should withdraw the objection to Claims 104 and 121.

The Examiner alleges Claims 107 and 124 recite a vague and indefinite phrase of "wherein the antisense oligonucleotide is antisense to the initiation codon, the coding region or the 5' or 3' intron-exon junctions of a gene encoding bradykinin b2 receptor." Applicant has amended Claims 107 and 124 to read "wherein the antisense oligonucleotide is antisense to the initiation codon, the coding region or the 5' or 3' intron-exon junctions of a [[gene]] nucleic acid encoding bradykinin b2 receptor," which obviates the rejection. Therefore, the Examiner should withdraw the objection to the claims.

35 U.S.C. § 112, 1st paragraph, § 103 Rejections

The Examiner has rejected pending claims 92-125 for allegedly not reasonably conveying to one of ordinary skill in the art that Applicant had possession of the claimed invention under 35 U.S.C. § 112, 1st paragraph.

As a preliminary matter, Applicant respectfully points out the claims were previously allowed on more than 5 occasions in a parent application (U.S. Serial No. 09/093,972; see comparison below). As can be seen in the tables below, the claims are substantially similar, with additional limitations added to the pending claims over the previously allowed claims. In addition, Applicant respectfully points out that the instant application is a continuation-in-part of the aforementioned parent application and includes the same disclosure, plus added data and disclosure as to a plurality additional oligonucleotides within the scope of the claims. The specification in the instant application, therefore, is substantially more extensive than the parent application. Applicant respectfully requests that the Examiner takes this fact into consideration in weighing the arguments in the instant application.

COMPARISON OF THE CLAIMS AT ISSUE – METHOD CLAIM:

PATENT APPLICATION NO.	09/093,972	09/543,679
CLAIM NUMBER	173 (See Exhibit A)	92
ORIGIN OF CLAIM	Supplemental Amendment – 3/28/2001	Currently Amended Claims (see above)
CLAIM LANGUAGE: PREAMBLE	An in vivo method of delivering a pharmaceutical composition to a target polynucleotide, comprising	An in vivo method of delivering a pharmaceutical composition to a target polynucleotide comprising
ELEMENT 1	Administering to the airways of a subject an aerosol composition of particle size about 0.5 u to about 500 u	administering to the airways of a subject said pharmaceutical composition of a respirable nebulizable particle size of 0.5 um to 10 um in size or 10 um to 500 um in size

ELEMENT 2	**comprising a nucleic acid which comprises at least one oligonucleotide (oligo)**	**comprising at least one antisense oligonucleotide**
ELEMENT 3	**effective to alleviate hyper-responsiveness to, and/or increased levels of, adenosine, or to alleviate bronchoconstriction, asthma and/or lung allergy(ies) and/or inflammation,**	**effective to alleviate hyper-responsiveness to adenosine or increased levels of adenosine, or to alleviate bronchoconstriction, asthma, or lung allergy,**
ELEMENT 4	**the oligo containing up to and including about 15% adenosine (A),**	**wherein the oligonucleotide is 7 to 60 nucleotides long and up to and including about 15% adenosine.**
ELEMENT 5	**and being anti-sense to the initiation codon, the coding region of the 5' and 3' intron-exon junctions of a gene encoding a protein associated with hyper-responsiveness, to and/or increased levels of, adenosine, bronchoconstriction, asthma and/or lung allergy(ies) and/or inflammation, or being anti-sense to the corresponding mRNA;**	**and the oligonucleotide is antisense to the initiation codon, the coding region of the 5' and 3' intron-exon junctions of a gene encoding a protein associated with hyper-responsiveness, to and/or increased levels of, adenosine, bronchoconstriction, asthma and/or lung allergy(ies) and/or inflammation, or being antisense to the corresponding mRNA thereof**
ELEMENT 6	**the nucleic acid comprising one or more oligo(s), pharmaceutically or veterinarily acceptable salts of the oligo(s), mixtures of the oligo(s) or their salts.**	**the nucleic acid comprising one or more oligonucleotide(s), pharmaceutically or veterinarily acceptable salts of the oligonucleotide(s), mixtures of the oligonucleotide(s) or their salts.**
DATES ALLOWED	**March 23, 2001 (Exh. B) March 26, 2001 (Exh. C) April 25, 2001 (Exh. D) May 24, 2001 (Exh. E) June 8, 2001 (Exh. F)**	**N/A**

COMPARISON OF THE CLAIMS AT ISSUE – PHARMACEUTICAL COMPOSITION CLAIM:

PATENT APPLICATION NO.	09/093,972	09/543,679
CLAIM NUMBER	108	109
ORIGIN OF CLAIM	Supplemental Amendment – 3/28/2001	Currently Amended Claims (see above)
CLAIM LANGUAGE: PREAMBLE	A pharmaceutical composition comprising	A pharmaceutical composition comprising
ELEMENT 1	a carrier	
ELEMENT 2	a nucleic acid in the form of an aerosol	wherein said pharmaceutical composition is of a [redacted] size of 0.5 μm to 10 μm in size or 10 μm to 500 μm in size.
ELEMENT 3	that comprises one or more oligonucleotides(s) (oligo(s)) effective to alleviate hyper-responsiveness to, and/or increased levels of, adenosine, bronchoconstriction, lung allergy(ies) and/or inflammation	at least one antisense oligonucleotide that is antisense to a target polynucleotide and when delivered to the airways of a subject is effective to alleviate hyper-responsiveness to adenosine or increased levels of adenosine, or to alleviate bronchoconstriction, asthma, or lung allergy,
ELEMENT 4	and contains up to and including about 15% adenosine (a)	wherein the oligonucleotide is 7 to 60 nucleotides long and comprises 15% or less adenosine,
ELEMENT 5	the oligo being anti-sense to an initiation codon, a coding region or a 5' or 3' intron-exon junctions of a gene encoding an adenosine A1, A2a, A2b or A3 receptor or anti-sense to their respective mRNA;	wherein the oligonucleotide is antisense to an initiation codon, a coding region or a 5' or 3' intron-exon junctions of a gene encoding an adenosine A1, A2a, A2b or A3 receptor or anti-sense to their respective mRNA thereof,
ELEMENT 6	pharmaceutically and veterinarily acceptable salts of the oligo(s) or mixtures thereof;	and comprises pharmaceutically and veterinarily acceptable salts of the oligo(s) or

		mixtures thereof
ELEMENT 7	**a surfactant that may be operatively linked to the nucleic acid**	**and comprises a surfactant that may be operatively linked to the nucleic acid**
DATES ALLOWED	**March 23, 2001 (Exh. B) March 26, 2001 (Exh. C) April 25, 2001 (Exh. D) May 24, 2001 (Exh. E) June 8, 2001 (Exh. F) July 23, 2001 (Exh. G)**	**N/A**

35 U.S.C. § 112, 1st Paragraph Rejection

The Examiner rejected Claims 92-125 for allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey that one had possession of the claimed invention. This rejection is respectfully traversed.

The Examiner alleges that the specification does not reasonably provide enablement for the treatment of hyper-responsiveness to adenosine or increased levels of adenosine, or to alleviate bronchoconstriction, asthma, or lung allergy by the administration of antisense oligonucleotides targeting any other mRNA target.

Response

Applicant respectfully asserts that Claims 92-125 are fully enabled by the teachings of the specification. As support, Applicant has submitted a signed declaration by Dr. Cynthia B. Robinson that clearly demonstrates that antisense oligonucleotides that are complementary to genes other than an adenosine receptor are also effective in reducing expression of these genes thereby treating a pulmonary disease. The Robinson Declaration provides data to show that oligonucleotides that are antisense to Bradykinin b2 receptor, eotaxin and interleukin 4 and 9 receptors, are effective for treating a respiratory disease or disorder. This information was in the specification as filed, and the information submitted by the declaration was within the scope of the claims as filed. Therefore the specification enables an in vivo method of delivering a pharmaceutical composition to a target polynucleotide comprising administering to the airways of a subject an antisense oligonucleotide in a pharmaceutical composition of particle size of 0.5 μm to 10 μm in size or 10 μm to 500 μm in size.

The Examiner also states that Krieg et al. refutes applicants claims when the prior art presents evidence that the claim cannot be enabled. Applicant respectfully points out that the Supplemental Amendment addressing the Examiner's concerns regarding Krieg et al. (U.S. Patent No. 6,207,646; see page 12 of the Supplemental Amendment) was previously filed and the Examiner failed to consider or comment on these arguments in the Supplemental Amendment. In the Supplemental Amendment, Applicant asserted that the '646 Krieg patent is not within the scope of the present claims because the specification teaches away from the instantly claimed invention. The '646 patent discloses examples using such oligonucleotides in cell cultures (for example, col. 39-41, example 10) and also by injection of such oligonucleotides into mice to prevent development of an inflammatory cellular infiltrate and eosinophilia in a murine model of asthma (col. 42, example 12). The '646 patent does not disclose the use of any antisense oligonucleotide and therefore, contrary to the Examiner's assertions, cannot render the claim not enabled because it does not fall within the scope of the claims.

35 U.S.C. § 103 Rejection

The Examiner rejected Claims 92-106, 108-123 and 125 as allegedly being unpatentable over Krieg et al. in view of Jacobsen et al, Debs et al. and Burns et al., and Claims 92-106, 108-123 and 125 as allegedly being unpatentable over Schreiber et al. in view of Debs et al. and Burns et al. Applicant respectfully asserts that Claims 92-125 are novel and non-obvious over all cited prior art references.

Response

It is recognized that a claim for a known substance which differs from the prior art only in degree, as for example in size or form, may not be patentable. An exception to this view has been made when a compound or composition possesses a specific activity that is greater than a prior art compound or composition and such was unpredictable from the prior art, then the compound or composition has been found patentable. The courts have looked for significant, advantageous unexpected differences. *In re Lunsford*, 148 U.S.P.Q. 716 (CCPA 1966). The court stated that "in all section 103 cases, we must look first to the *differences* between the prior art and the subject matter sought to be patented and then determine if what appellant did, or made, *as a whole*, would have been obvious." *Id.* at 720 (emphasis in the original).

Factors to be considered in determining whether an old product in a new form is obvious

over the prior art include (1) whether the claimed chemical compound or composition has the same utility as closely related materials in the prior art, and (2) whether the prior art suggests the particular form or structure of the claimed material or suitable methods of obtaining that form or structure. *In re Cofer*, 148 U.S.P.Q. 268 (CCPA 1966) (claims to the free-flowing crystalline form of a compound were held unobvious over references disclosing the viscous liquid form of the same compound because the prior art of record did not suggest the claimed compound in crystalline form or how to obtain such crystals).

The use of antisense oligonucleotides in the small particle form is novel and non-obvious in that the administration of antisense oligonucleotides in the small particle form to a subject's lungs provides for unexpectedly superior results of efficacy. The Robinson Declaration shows that the claimed methods of treatment using antisense oligonucleotides in small particle sizes and the claimed pharmaceutical compositions of antisense oligonucleotides in small particle sizes provides superior results in treating respiratory diseases and disorders. The treatment of diseases by use of antisense oligonucleotides has the potential of being administered in a variety of means. Typically, such administration is in the form of injection, as this mode of administration has been used by investigators for treatment of diseases using antisense oligonucleotides. This mode of administration permits controlled administration of the drug and potential systemic treatment of a target disease. However, recent studies (subsequent to the effective filing date of the present invention) have shown that injection or oral administration of drugs to treat respiratory diseases such as asthma have not been effective (e.g., use of dehydroepiandrosterone for the treatment of asthma). Direct administration of drugs to the airways may be problematical in controlling the dosage and proper adsorption of the drug at the site. The results obtained using the present invention show the superiority of treating respiratory diseases by controlling the particle size of the drug and administering the drug directly to the airway of the patient over the systemic treatment. The Robinson Declaration shows that the claimed invention provides superior results of efficacy as compared to the results one would expect if the oral or injectable treatment were used. Specifically, by providing small particle size of 1-5 μm for small airway deposition or 0.5 μm to 500 μm for upper airway deposition one is able to achieve a higher concentration of the antisense oligonucleotide drug at the specific locality where it is to interact with its target polynucleotides. The cited prior art neither teaches nor suggests such advantages.

Moreover, Applicant respectfully points out that the Supplemental Amendment filed

November 11, 2003 addressed the Examiner's concerns regarding Krieg et al. (U.S. Patent No. 6,207, 646) and Debs et al. (U.S. Patent No. 6,001,644). The Examiner failed to consider or even comment on the arguments presented in the Supplemental Amendment, which clearly show why the combination of Krieg et al., in view of Jacobsen et al., Debs et al. and Burns et al., or Schreiber et al., in view of Debs et al. and Burns et al. fails to render obvious the instantly claimed invention.

In regard to the alleged combination of references, the Examiner fails to set forth prima facie evidence or argument that the combination of references renders the instantly claimed invention obvious. In order to make a showing of obviousness under 35 U.S.C. § 103(a), the Examiner must: (1) consider the claimed invention as a whole; 2) the references "must suggest the desireability and thus the obviousness of making the combination"; 3) the Examiner cannot view the references using the benefit of "impermissible hindsight vision"; and 4) the Examiner must apply "a reasonable expectation of success" standard when viewing the application. MPEP § 2141 "35 U.S.C. 103; the Graham Factual Inquiries". When considering the claimed invention as a whole, a proper combination of references must first and foremost comprise all of the elements of the instantly claimed invention.

In view of these requirements, the Examiners' assertions respectfully do not comport with the requirements of a prima facie case of obviousness showing under 35 U.S.C. § 103(a). Firstly, the combination of the alleged prior art references do not disclose all of the elements of the claimed invention. For example, Debs et al. (the '644 patent) teaches away from the instantly claimed invention and therefore does not render obvious the claimed invention. The '644 patent discloses a method for treating cystic fibrosis by introducing a construct into the lung cells of a mammal and expressing a nucleic acid from the construct in the lungs of the mammal, wherein the nucleic acid may be an antisense strand of DNA (col. 4, lines 17-32).

The disclosure of the '644 patent teaches away from the instant application and therefore does not render obvious the claimed invention for the following five reasons:

1) The '644 patent discloses a method whereby a construct is administered to a mammal and the construct expresses an antisense strand DNA in the lung. The presently claimed invention is directed a method whereby the antisense oligonucleotide itself is administered into the lung, and a pharmaceutical composition comprising an antisense oligonucleotide, i.e. the antisense oligonucleotide is <u>not</u> expressed in the cells of the patient.

2) The '644 patent discloses a method for <u>increasing</u> the expression of a gene, specifically

the gene encoding the CFTR protein. The presently claimed invention is directed to a method and a pharmaceutical composition for reducing the expression of a gene, the opposite of the '644 patent.

3) Besides "a defective or mutant CFTR gene" (col. 27, lines 51-54), the '644 patent does not disclose the specific target gene that an antisense strand DNA is to target. The presently claimed invention is directed a method and a pharmaceutical composition whereby the antisense oligonucleotide targets a polynucleotide that results in alleviating hyper-responsiveness to adenosine or increased levels of adenosine, or to alleviate bronchoconstriction, asthma, or lung allergy. Specifically, the presently claimed invention provides a list of more than 160 proteins involved in a pulmonary disease or condition (pages 9-10). The genes encoding these proteins are targets for the claimed antisense oligonucleotides. In addition, the genes are neither defective nor mutant.

4) The '644 patent does not disclose an antisense oligonucletide that comprises 15% or less adenosine.

5) The '644 patent is not enabling for a method of administering small particle size antisense DNA into the lungs for treating a lung disease or disorder. In contrast to the presently claimed invention application, the '644 patent does not provide any experimental data to demonstrate the efficacy of alleviating a lung disease or disorder by administering a small particle size to a patient.

Therefore, the '644 patent does not render the claimed invention obvious, because the combination of Debs et al. with Schreiber et al. and Burns et al. does not disclose all of the elements of the claimed invention. Moreover, one of ordinary skill in the art relying on Debs et al. would have not a reasonable expectation of success in treating a lung disease or disorder by administering an antisense oligonucletide of a small particle size comprising 15% or less adenosine. The rejection to Claims 92-106, 108-123 and 125 in view of Schreiber et al., Debs et al. and Burns et al. should be withdrawn.

Applicant also respectfully asserts that the '646 patent (Krieg et al.) neither anticipates nor renders obvious the claimed invention. As pointed out in the previously filed Supplemental Amendment, the '646 patent discloses using immunostimulatory oligonucleotides containing CpG unmethylated dinucleotides to redirect a Th2 response to a Th1 response. The '646 patent discloses examples using such oligonucleotides in cell cultures (for example, col. 39-41, Example 10) and also by **injection** of such oligonucleotides into mice to prevent development of an inflammatory

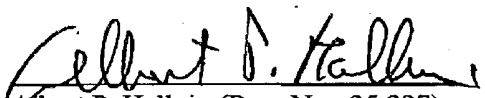
cellular infiltrate and eosinophilia in a murine model of asthma (col. 42, Example 12). The '646 patent does not disclose the use of any antisense oligonucleotide, and therefore the combination of references fails to disclose all of the elements of the claimed invention. Further, the '646 patent teaches away from the claimed invention because the '646 patent discloses administering the oligonucleotides by injection. Therefore, the '646 patent does not render the claimed invention obvious, because one of ordinary skill in the art relying on the '644 would have not a reasonable expectation of success in treating a lung disease or disorder by administering an antisense oligonucletide of a small particle size comprising 15% or less adenosine by means of inhalation.

CONCLUSION

Applicant believes that the application is in good and proper condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 463-8109.

Respectfully submitted,

Date: April 13, 2004



Albert P. Halluin (Reg. No. 25,227)
Lorelei P. Westin (Reg. No. 52,353)

HOWREY SIMON ARNOLD & WHITE, LLP
301 Ravenswood Avenue
Box 34
Menlo Park, CA 94025
(650) 463-8109